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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,016	08/30/2001	Carlos Martinez Alonso	46309-253995	8132

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,016	ALONSO ET AL.	
	Examiner	Art Unit	
	Christopher H. Yaen	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-40,58 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-40,58 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Re: Alonso *et al*

1. The amendment filed 1/3/2005 is acknowledged and entered into the record. Accordingly, claims 1-36,41-57, and 59-60 are canceled without prejudice or disclaimer.

2. Claims 37-40, 58, and 61 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

4. The rejection of claims 37-39, 58, 61 and now newly amended claim 40 under 35 USC § 112, 1st paragraph as lacking written description is maintained for the reasons of record. Applicant argues that the skilled artisan would be capable of visualizing the claimed variants and alleles of the recited sequences (i.e. SEQ ID Nos: 1-3) because one of skill in the art could easily screen for sequences that have the same or similar functional activities or properties. Specifically, applicant contends that mutations to the recited sequences could be made without altering the function of the claimed protein and that such modifications could be made with reasonable accuracy, wherein the skilled artisan could easily predict whether the function would be altered. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

To satisfy the requirements of written description for a genus claim, a sufficient disclosure of structural and functional characteristics coupled with a known or disclosed

correlation between function and structure is required. In the instant case, applicant has not described any common characteristics, by way of common structure or disclosing a correlation between function and structure so that the skilled artisan could identify them as members of a genus. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. Since the applicant has only disclosed sequences of SEQ ID No: 1,2, 3 and no other, the written description for variants or alleles is not adequately supported. Moreover, the specification of the instant applicant teaches that the DIO-1 is a novel gene/protein that is involved in the apoptosis pathway. The specification also teaches that the DIO-1 gene/protein is up-regulated in cells that are undergoing apoptosis and that when transfected into cells, caused cells to undergo apoptosis. However, what the specification has failed to provided is the specific functional activity of the claimed gene/protein. Absent this functional activity, the skilled artisan cannot readily screen for "functional equivalents" of the claimed DIO-1 gene/protein. Therefore, claiming a genus of molecules by recitation of an unknown functional is inadequate to describe the instantly claimed genus of variants and alleles. The skilled artisan thus cannot envision the detailed chemical structure of the encompassed genus of polynucleotides or protein nor ahs the applicant correlated a structure with a known function. Finally, the general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed.

Therefore, the rejection of claims as lacking written description is maintained for the reasons of record.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

5. The rejection of claims 58 and 61 under 35 USC § 112, 1st paragraph as lacking an enabling disclosure is maintained for the reasons of record. Applicant argues that the disclosed in vitro experiments presented are representative of in vivo situations. Specifically, applicant argues that the *in vitro* model of a chicken limb is representative of *in vivo* application and that one skilled in the art could easily use the disclosed information to practice the instantly claimed invention without undue experimentation. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

Reasonable guidance between what is claimed and what is taught in the specification must be provided in order for one of skill in the art to practice the invention without undue experimentation. In the instant case, one of skill in the art cannot reasonable extrapolate the teachings of the specification (i.e. gene thereapy) to that of the claims (i.e. protein/peptide administration). The applicant indicates that a chicken limb assay would be indicative of *in vivo* success, however, the example provided uses retroviral vectors containing a nucleotide sequence which encodes a DIO-1 molecule. The use of nucleotide vectors is neither correlative nor indicative of the effects of administering peptides or proteins to an individual.

Moreover, it is well established in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2).

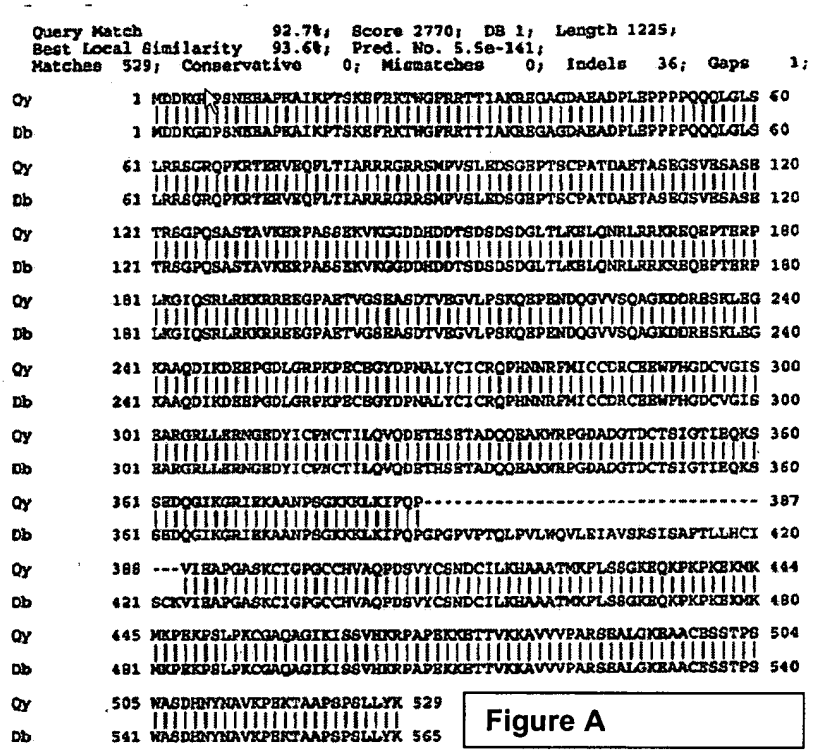
Therefore, given the lack of correlation between gene therapy and peptide administration and the unpredictable nature of peptide chemistry in general, one of skill in the art cannot reasonable practice the invention commensurate in scope to the claims given the disclosure of the instant application.

Claim Rejections Maintained - 35 USC § 102

6. The rejection of claims 37-39, 61 and now newly amended claim 40 under 35 USC § 102(b) as being anticipated by Nagase *et al* (DNA Res. 1997;4(2):141-150) is maintained for the reasons of record. Applicant argues that the cited reference of Nagase *et al* does not teach each and every limitation of the claimed invention. Specifically, applicant argues that the protein of Nagase *et al*, if expressed would most likely fail. Applicant attributes the failure to improper folding and degradation by "quality control" proteases. Applicant additionally, contends that even if the protein were functional, the protein would most likely not have the same or similar function of the claimed sequence. Applicant goes on to contend that given the disclosure of Nagase *et al* the skilled artisan would be required to undergo large amounts of experimentation in order for the claimed invention to be identified. Applicant concludes by indicating that Nagase *et al* does not provide an enabling disclosure. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

First, it is noted that the claimed invention is drawn in part to functional variants of the claimed amino acid sequences (i.e. SEQ ID No: 1 and 3). Although it is clear that

the sequence taught by Nagase *et al* is not 100% identical to the claimed and recited sequences of SEQ ID No: 1 or 3, for the purposes of examination, the term "variant" has been interpreted as defined in the specification (see page 2, line 12-13) as being



"derived from a sequences given in the figures." Thus given the significant overlap between the sequence of SEQ ID No: 3 and that disclosed by Nagase *et al* (**see figure A**), the sequence disclosed by Nagase *et al* is encompassed by the claims.

Moreover, the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). In the instant case, applicant's arguments concerning the function and activity of the disclosed sequence of Nagase *et al* is not germane nor pertinent to rebut the *prima facie* case of anticipation. Absent objective evidence to the contrary, the function of the prior art disclosed sequence would have the same functional characteristics as the claimed DIO-1 polypeptide and its variants, because such functions or activities are inherent to the

polypeptide itself. Thus, applicant's arguments, are at best, speculative and does not overcome the rejection. Lastly, when the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. *In re Sasse*, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). In the instant case, applicant submits speculative arguments that are not considered factual, and therefore, the reference is still considered enabling and anticipatory.

Applicant additionally compares the sequence of SEQ ID No: 4 with that of Nagase *et al.* Applicant's arguments are substantially similar to those argued above.

The rejection of claims under 35 USC 102(b) as being anticipated is maintained for the reasons of record.

All other rejections are withdrawn in view of the applicant's amendments and arguments thereto as set forth in a paper filed 1/3/2005.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H. Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1643
June 29, 2005

SHEELA HUFF
PRIMARY EXAMINER